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(54) Process for reducing the crystal size of ondansetron hydrochloride dihydrate.

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EP-A- 0 275 668
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Description

This invention relates to a process for reducing the crystal size of ondansetron hydrochloride dihydrate. More particularly the process involves desolvation and resolvation.

Reduction of crystal size through solvation and desolvation has been described previously, for instance for the compound griseofulvin (K. Sekiguchi et al., Chem. Pharm. Bull., 1968, 16, 2495-2502). Various techniques may be employed to effect desolvation such as drying at an elevated temperature and under vacuum, drying at an elevated temperature and at atmospheric pressure, drying at ambient temperature under a high vacuum, freeze-drying, or drying over a desiccant. However, the precise conditions of desolvation considerably affect the efficiency of the reduction in crystal size.

Ondansetron, the approved name for 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one, is a highly selective and potent antagonist of 5-hydroxytryptamine (5-HT) at 5-HT_3 receptors. Ondansetron, together with its physiologically acceptable salts and solvates, is described and claimed in British Patent No. 2153821B, and may be used in the treatment of a variety of conditions, including the nausea and vomiting induced by cancer chemotherapy and radiotherapy (as described, for example, in European Patent Specification No. 226266A).

The preferred form of ondansetron for pharmaceutical formulation is the hydrochloride dihydrate. Ondansetron hydrochloride dihydrate may be presented in a variety of formulations, one of which is as tablets for oral administration, when particularly suitable unit doses of the drug substance for the treatment of emesis are 5mg and 10mg.

In the tablet manufacturing process, ondansetron hydrochloride dihydrate is blended with suitable excipients, and the blend is then compressed into tablets.

Since a low dose of drug substance per tablet is required, for example, 5mg of ondansetron hydrochloride dihydrate in a tablet of 125mg compression weight, the distribution of the drug substance in the blend is critical in obtaining individual tablets with the correct drug content. Uniform drug distribution in the tablet blend may be achieved using drug substance of appropriate particle size. However, the ondansetron hydrochloride dihydrate obtained by methods described in the art, i.e. that obtained by simple crystallisation from an aqueous solvent mixture with subsequent drying at ambient temperature and pressure contains particles which are too large (i.e. >250μm) to give an homogeneous distribution of the drug substance in the tablet blend. Indeed if crystalline ondansetron hydrochloride dihydrate produced by such conventional methods were used in tablet manufacture, the tablets so produced would not possess an acceptable drug content which, for a 5mg tablet, is 5mg ± 0.25mg of ondansetron hydrochloride dihydrate.

Attempts to mill crystals of ondansetron hydrochloride dihydrate to reduce their particle size have proved unsuccessful, for example, comminution milling of ondansetron hydrochloride dihydrate caused screen blockage of coarse and fine screens. Furthermore, although ondansetron hydrochloride dihydrate of particle size <250μm can be obtained by passing the substance through a 60 mesh sieve (as described, for example, in UK Patent No. 2153821B), this method is not commercially viable.

We have now found a process which reduces the crystal size of ondansetron hydrochloride dihydrate produced by simple crystallisation from solvent (more particularly aqueous solvent mixtures) to a size which is suitable for effective distribution of the drug substance in the tablet blend.

Thus the invention provides a process for reducing the crystal size of ondansetron hydrochloride dihydrate obtained by simple crystallisation from solvent, more particularly an aqueous solvent mixture, to a size which is suitable for effective distribution in a tablet blend, which comprises desolvating the said drug substance by drying at an elevated temperature and reduced or atmospheric pressure, and then rehydrating the ondansetron hydrochloride so formed.

It is possible by means of the process according to the invention to reduce the crystal size of ondansetron hydrochloride dihydrate to the extent that the entire drug substance consists of particles of a sufficiently small size (i.e. less than 250μm, of which typically about 80% by weight are less than 63μm) to give an homogeneous distribution of the drug substance in the tablet blend.

Preferably, the ondansetron hydrochloride dihydrate obtained by crystallisation is desolvated by heating at a temperature greater than 40 °C (e.g. 50 °C) and at reduced pressure (e.g. 26.664 x 10^3 Pa (200 torr) or less) for more than 8 hours. Alternatively, the ondansetron hydrochloride dihydrate obtained by crystallisation may be desolvated at ambient pressure by heating at a temperature of 50 °C or above (more preferably 100 °C).

Most preferably, ondansetron hydrochloride dihydrate obtained by crystallisation is desolvated by heating at 50 °C at a pressure of 100 torr for 24 hours.

The desolvation process may be carried out with or without mechanical agitation.

The resultant ondansetron hydrochloride of reduced crystal size is then rehydrated, for example, by placing it in a humidified atmosphere of, for example, air or nitrogen, at ambient temperature. Rehydration will generally be continued until there is no further gain in weight.

According to another aspect, the invention provides crystalline ondansetron hydrochloride dihydrate characterised in that 100% of the crystals have a size of less than 250µm and at least 80% by weight of the crystals have a crystal size of less than 63µm (as measured by air-jet sieve analysis).

According to a yet further aspect, the invention provides a pharmaceutical composition in the form of tablets containing crystalline ondansetron hydrochloride dihydrate as active ingredient characterised in that 100% of the ondansetron hydrochloride dihydrate crystals have a size less than 250µm and at least 80% by weight of the crystals have a crystal size of less than 63µm (as measured by air-jet sieve analysis). Generally the composition will contain at least one physiologically acceptable carrier or excipient.

The invention is illustrated by the following examples. Temperatures are in °C. Crystal size was measured by air-jet sieve analysis.

Example 1

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate wherein the crystals are less than 250µm

A solution of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one (147g) in a mixture of isopropanol (670mℓ), water (250mℓ) and glacial acetic acid (76mℓ) at ca. 60° was clarified by filtration and diluted with more water (61mℓ) and isopropanol (650mℓ). The solution was treated at 70° with 36%w/w hydrochloric acid (46mℓ) and cooled to ca. 5°. The resulting suspension was filtered and the filtered solid was washed by displacement with isopropanol (600mℓ) to give a solvent wet solid (269g). A portion of this solid (91g) was dried at ca. 50° and 200 torr for ca. 16h to give a solid (55g).

A portion of the dried solid (26g) was placed in a current of humidified air at ambient temperature until there was no further gain in weight and the title compound (29g) was obtained.

Particle Size Distribution of Title Compound	
Size (µm)	Cumulative % Undersize (by weight)
45	43.4
63	83.7
90	97.6
125	98.4
180	99.6
250	100.0

Example 2

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate wherein the crystals are less than 250µm

The previous preparation was repeated except that after collection by filtration the solid was dried at ambient temperature and pressure to give large crystals (>45% by weight of crystals larger than 250µm) of 1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate.

Particle Size Distribution of "Large Crystals"	
Size(μm)	Cumulative % Undersize (by weight)
45	5.8
63	9.8
90	20.8
125	26.7
180	37.8
250	50.6
355	71.5
500	90.9
710	98.4
1000	98.6

A sample of this solid (26.9g) was dried at ambient pressure and 100° for ca. 17h during which period the weight of the sample was reduced to 24.3g. The sample was then exposed to ambient temperatures and humidities until it had regained its original weight to afford the title compound.

Particle Size Distribution of Title Compound	
Size (μm)	Cumulative % Undersize (by weight)
45	47.6
63	94.8
90	100.0

Example 3

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate wherein the crystals are less than 250μm

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate obtained by crystallisaton from a solvent was dried at 52° and 13.332 x 10^3 Pa (100 torr) for 24h and then rehydrated to give the title compound.

Particle Size Distribution of Title Compound	
Size (μm)	Cumulative % Undersize (by weight)
45	44.3
63	83.2
90	97.0
125	98.8
180	99.8
250	100.0

Example 4

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate wherein the crystals are less than 90μm

1,2,3,9-Tetrahydro-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-4H-carbazol-4-one hydrochloride dihydrate obtained by crystallisaton from a solvent was dried at 48° and 13.332 x 10^3 Pa (100 torr) for 24h and then rehydrated to give the title compound.

Particle Size Distribution of Title Compound	
Size (μm)	Cumulative % Undersize
45	49.0
63	92.4
90	100.0

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. A process for reducing the crystal size of ondansetron hydrochloride dihydrate produced by crystallisation from solvent, characterised in that the ondansetron hydrochloride dihydrate is desolvated by drying at elevated temperature and reduced or atmospheric pressure and then rehydrated.

2. A process as claimed in claim 1, characterised in that the ondansetron hydrochloride dihydrate is prepared by crystallisation from an aqueous solvent mixture.

3. A process as claimed in claim 1 or 2, characterised in that the ondansetron hydrochloride dihydrate is desolvated by heating at a temperature greater than 40°C and at reduced pressure for more than 8 hours.

4. A process as claimed in claim 3, characterised in that the ondansetron hydrochloride dihydrate is desolvated by heating at a temperature of about 50°C at a pressure of about 13.332 x 10^3 Pa (100 torr) for about 24 hours.

5. A process as claimed in claim 1 or 2, characterised in that the ondansetron hydrochloride dihydrate is desolvated by heating at a temperature of 50°C or above at ambient pressure.

6. A process as claimed in claim 5, characterised in that the temperature is about 100°C.

7. A process as claimed in any of claims 1 to 6, characterised in that the ondansetron hydrochloride dihydrate is rehydrated in a humidified atmosphere at ambient temperature.

8. Crystalline ondansetron hydrochloride dihydrate characterised in that 100% of the crystals have a size of less than 250μm and at least about 80% by weight of the crystals have a size of less than 63μm.

9. A pharmaceutical composition in the form of tablets containing crystalline ondansetron hydrochloride dihydrate as active ingredient, characterised in that 100% of the ondansetron hydrochloride dihydrate crystals have a size less than 250μm and at least about 80% by weight of the crystals have a size less than 63μm.

10. A pharmaceutical composition as claimed in claim 9, characterised in that each tablet has a nominal content of active ingredient which is 5mg or 10mg.

Claims for the following Contracting States : ES, GR

1. A process for reducing the crystal size of ondansetron hydrochloride dihydrate produced by crystallisation from solvent, characterised in that the ondansetron hydrochloride dihydrate is desolvated by drying at elevated temperature and reduced or atmospheric pressure and then rehydrated.

2. A process as claimed in claim 1, characterised in that the ondansetron hydrochloride dihydrate is prepared by crystallisation from an aqueous solvent mixture.

3. A process as claimed in claim 1 or 2, characterised in that the ondansetron hydrochloride dihydrate is desolvated by heating at a temperature greater than 40 °C and at reduced pressure for more than 8 hours.

4. A process as claimed in claim 3, characterised in that the ondansetron hydrochloride dihydrate is desolvated by heating at a temperature of about 50 °C at a pressure of about 13.332 x 10^3 Pa (100 torr) for about 24 hours.

5. A process as claimed in claim 1 or 2, characterised in that the ondansetron hydrochloride dihydrate is desolvated by heating at a temperature of 50 °C or above at ambient pressure.

6. A process as claimed in claim 5, characterised in that the temperature is about 100 °C.

7. A process as claimed in any of claims 1 to 6, characterised in that the ondansetron hydrochloride dihydrate is rehydrated in a humidified atmosphere at ambient temperature.

8. A process for the manufacture of a pharmaceutical composition characterised in that crystalline ondansetron hydrochloride dihydrate wherein 100% of the crystals have a size less than 250µm and at least about 80% by weight of the crystals have a size less than 63µm is processed to form tablets.

9. A process as claimed in claim 8, characterised in that the crystalline ondansetron hydrochloride dihydrate is processed to form tablets with a nominal content of active ingredient which is 5mg or 10mg.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Verfahren zur Verringerung der Kristallgröße von Ondansetronhydrochloriddihydrat, welches durch Kristallisation aus einem Lösungsmittel hergestellt worden ist, dadurch **gekennzeichnet,** daß das Ondansetronhydrochloriddihydrat durch Trocknen bei erhöhter Temperatur und verringertem oder Atmosphärendruck desolvatisiert und dann rehydratisiert wird.

2. Verfahren nach Anspruch 1, dadurch **gekennzeichnet,** daß das Ondansetronhydrochloriddihydrat durch Kristallisation aus einem wäßrigen Lösungsmittelgemisch hergestellt worden ist.

3. Verfahren nach Anspruch 1 oder 2, dadurch **gekennzeichnet,** daß das Ondansetronhydrochloriddihydrat durch Erhitzen bei einer Temperatur über 40 °C und bei verringertem Druck während mehr als 8 Stunden desolvatisiert wird.

4. Verfahren nach Anspruch 3, dadurch **gekennzeichnet,** daß das Ondansetronhydrochloriddihydrat durch Erhitzen bei einer Temperatur von etwa 50 °C bei einem Druck von etwa 13,332 x 10^3 Pa (100 Torr) während etwa 24 Stunden desolvatisiert wird.

5. Verfahren nach Anspruch 1 oder 2, dadurch **gekennzeichnet,** daß das Ondansetronhydrochloriddihydrat durch Erhitzen bei einer Temperatur von 50 °C oder darüber bei Umgebungsdruck desolvatisiert wird.

6. Verfahren nach Anspruch 5, dadurch **gekennzeichnet,** daß die Temperatur etwa 100 °C beträgt.

7. Verfahren nach einem der Ansprüche 1 bis 6, dadurch **gekennzeichnet,** daß das Ondansetronhydrochloriddihydrat in einer angefeuchteten Atmosphäre bei Umgebungstemperatur rehydratisiert wird.

8. Kristallines Ondansetronhydrochloriddihydrat, dadurch **gekennzeichnet,** daß 100% der Kristalle eine Größe von weniger als 250 µm und mindestens etwa 80 Gew.-% der Kristalle eine Größe von weniger als 63 µm besitzen.

9. Pharmazeutische Zusammensetzung in Form von Tabletten, die kristallines Ondansetronhydrochloriddihydrat als aktiven Bestandteil enthält, dadurch **gekennzeichnet,** daß 100% der Ondansetronhydrochloriddihydrat-Kristalle eine Größe von weniger als 250 µm und mindestens etwa 80 Gew.-% der Kristalle eine Größe von weniger als 63 µm besitzen.

10. Pharmazeutische Zusammensetzung nach Anspruch 9, dadurch **gekennzeichnet,** daß jede Tablette einen nominalen Gehalt an aktivem Bestandteil besitzt, der 5 mg oder 10 mg beträgt.

Patentansprüche für folgende Vertragsstaaten : ES, GR

1. Verfahren zur Verringerung der Kristallgröße von Ondansetronhydrochloriddihydrat, welches durch Kristallisation aus einem Lösungsmittel hergestellt worden ist, dadurch **gekennzeichnet,** daß das Ondansetronhydrochloriddihydrat durch Trocknen bei erhöhter Temperatur und verringertem oder Atmosphärendruck desolvatisiert und dann rehydratisiert wird.

2. Verfahren nach Anspruch 1, dadurch **gekennzeichnet,** daß das Ondansetronhydrochloriddihydrat durch Kristallisation aus einem wäßrigen Lösungsmittelgemisch hergestellt worden ist.

3. Verfahren nach Anspruch 1 oder 2, dadurch **gekennzeichnet,** daß das Ondansetronhydrochloriddihydrat durch Erhitzen bei einer Temperatur über 40 °C und bei verringertem Druck während mehr als 8 Stunden desolvatisiert wird.

4. Verfahren nach Anspruch 3, dadurch **gekennzeichnet,** daß das Ondansetronhydrochloriddihydrat durch Erhitzen bei einer Temperatur von etwa 50 °C bei einem Druck von etwa 13,332 x 10^3 Pa (100 Torr) während etwa 24 Stunden desolvatisiert wird.

5. Verfahren nach Anspruch 1 oder 2, dadurch **gekennzeichnet,** daß das Ondansetronhydrochloriddihydrat durch Erhitzen bei einer Temperatur von 50 °C oder darüber bei Umgebungsdruck desolvatisiert wird.

6. Verfahren nach Anspruch 5, dadurch **gekennzeichnet,** daß die Temperatur etwa 100 °C beträgt.

7. Verfahren nach einem der Ansprüche 1 bis 6, dadurch **gekennzeichnet,** daß das Ondansetronhydrochloriddihydrat in einer angefeuchteten Atmosphäre bei Umgebungstemperatur rehydratisiert wird.

8. Verfahren zur Herstellung eines pharmazeutischen Präparats, dadurch **gekennzeichnet,** daß kristallines Ondansetronhydrochloriddihydrat, wobei 100% der Kristalle eine Größe von weniger als 250 µm und mindestens etwa 80 Gew.-% der Kristalle eine Größe von weniger als 63 µm besitzen, unter Bildung von Tabletten verarbeitet wird.

9. Verfahren nach Anspruch 8, dadurch **gekennzeichnet,** daß das kristalline Ondansetronhydrochloriddihydrat unter Bildung von Tabletten verarbeitet wird, die einen nominalen Gehalt an aktivem Bestandteil von 5 mg oder 10 mg aufweisen.

Revendications
Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE

1. Procédé pour diminuer la taille des cristaux d'ondansetron hydrochlorure dihydrate produit par cristallisation à partir de solvant, caractérisé en ce que l'ondansetron hydrochlorure dihydrate est désolvaté par séchage à température élevée et sous pression réduite ou à la pression atmosphérique, et ensuite réhydraté.

2. Procédé tel que revendiqué dans la revendication 1, caractérisé en ce que l'ondansetron hydrochlorure dihydrate est préparé par cristallisation à partir d'un mélange solvant aqueux.

3. Procédé tel que revendiqué dans la revendication 1 ou 2, caractérisé en ce que l'ondansetron hydrochlorure dihydrate est désolvaté par chauffage à une température supérieure à 40 °C et sous une pression réduite pendant plus de 8 heures.

4. Procédé tel que revendiqué dans la revendication 3, caractérisé en ce que l'ondansetron hydrochlorure dihydrate est désolvaté par chauffage à une température d'environ 50 °C sous une pression d'environ 13,332 x 10^3Pa (100 torr) pendant environ 24 heures.

5. Procédé tel que revendiqué dans la revendication 1 ou 2, caractérisé en ce que l'ondansetron hydrochlorure dihydrate est désolvaté par chauffage à une température de 50 °C ou au-dessus à la pression ambiante.

6. Procédé tel que revendiqué dans la revendication 5, caractérisé en ce que la température est d'environ 100 °C.

7. Procédé tel que revendiqué dans l'une quelconque des revendications 1 à 6, caractérisé en ce que l'ondansetron hydrochlorure dihydrate est réhydraté en atmosphère humide à la température ambiante.

8. Ondansetron hydrochlorure dihydrate en cristaux, caractérisé en ce que 100% des cristaux ont une taille de moins de 250 µm, et au moins environ 80% en poids des cristaux ont une taille inférieure à 63 µm.

9. Composition pharmaceutique sous la forme de comprimés contenant de l'ondansetron hydrochlorure dihydrate en cristaux comme ingrédient actif, caractérisée en ce que 100% des cristaux d'ondansetron hydrochlorure dihydrate ont une taille inférieure à 250 µm et au moins environ 80% en poids des cristaux ont une taille inférieure à 63 µm.

10. Composition pharmaceutique telle que revendiquée dans la revendication 9, caractérisée en ce que chaque comprimé contient une teneur nominale en ingrédient actif qui est de 5 mg ou de 10 mg.

Revendications pour les Etats contractants suivants : ES, GR

1. Procédé pour diminuer la taille des cristaux d'ondansetron hydrochlorure dihydrate produit par cristallisation à partir de solvant, caractérisé en ce que l'ondansetron hydrochlorure dihydrate est désolvaté par séchage à température élevée et sous pression réduite ou à la pression atmosphérique, et ensuite réhydraté.

2. Procédé tel que revendiqué dans la revendication 1, caractérisé en ce que l'ondansetron hydrochlorure dihydrate est préparé par cristallisation à partir d'un mélange solvant aqueux.

3. Procédé tel que revendiqué dans la revendication 1 ou 2, caractérisé en ce que l'ondansetron hydrochlorure dihydrate est désolvaté par chauffage à une température supérieure à 40 °C et sous une pression réduite pendant plus de 8 heures.

4. Procédé tel que revendiqué dans la revendication 3, caractérisé en ce que l'ondansetron hydrochlorure dihydrate est désolvaté par chauffage à une température d'environ 50 °C sous une pression d'environ 13,332 x 10^3Pa (100 torr) pendant environ 24 heures.

5. Procédé tel que revendiqué dans la revendication 1 ou 2, caractérisé en ce que l'ondansetron hydrochlorure dihydrate est désolvaté par chauffage à une température de 50 °C ou au-dessus à la pression ambiante.

6. Procédé tel que revendiqué dans la revendication 5, caractérisé en ce que la température est d'environ 100 °C.

7. Procédé tel que revendiqué dans l'une quelconque des revendications 1 à 6, caractérisé en ce que l'ondansetron hydrochlorure dihydrate est réhydraté en atmosphère humide à la température ambiante.

8. Procédé pour fabriquer une composition pharmaceutique, caractérisé en ce que de l'ondansetron hydrochlorure dihydrate en cristaux, dans lequel 100% des cristaux ont une taille inférieure à 250 µm et au moins environ 80% en poids des cristaux ont une taille inférieure à 63 µm est traité pour former des comprimés.

9. Procédé tel que revendiqué dans la revendication 8, caractérisé en ce que l'ondansetron hydrochlorure dihydrate est traité pour former des comprimés ayant une teneur nominale en ingrédient actif de 5 mg ou 10 mg.